

Loss of tubular creatinine secretion as the only sign of tubular proximal cell dysfunction in light chain proximal tubulopathy

A case report

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Abstract

Light chain proximal tubulopathy (LCPT) is a rare disease, characterized by cytoplasmic inclusions of light chain (usually kappa) immunoglobulins. Clinical presentation is usually a Fanconi syndrome. The proximal tubular dysfunction can be incomplete, and exceptional cases of LCPT without any tubular dysfunction have even been described. Here, we report a case of LCPT in which the only sign of proximal tubulopathy is the absence of secretion of creatinine, as assessed by the simultaneous measurement of renal clearance of creatinine and ⁵¹CrEDTA. The loss of tubular creatinine secretion as a sign of tubular proximal cell dysfunction ought to be identified in patients with light chain proximal tubulopathy as it leads to a clinically relevant underestimation of GFR by the creatinine-derived equations. The prevalence and prognostic significance of this particular proximal tubular damage in LCPT remain to be determined.

Abbreviations: 51CrEDTA = chromium- 51 ethylenediamine tetraacetic acid, CCr = creatinine clearance, CCr-S = part of creatinine clearance attributable to secretion, CKD EPI = chronic kidney disease—epidemiology collaboration, eGFR = estimated glomerular filtration rate, GFR = glomerular filtration rate, LCPT = light chain proximal tubulopathy, MATE = multidrug and toxin extrusion, MDRD = Modification of Diet in Renal Disease, mGFR = measured glomerular filtration rate, OCT2 = human organic cation transporter 2, TmPi/GFR = renal phosphate threshold normalized for the glomerular filtration rate.

Keywords: estimated GFR accuracy, Fanconi syndrome, light chain proximal tubulopathy, monoclonal gammopathy of renal significance, tubular creatinine secretion

1. Introduction

Light chain proximal tubulopathy (LCPT) is a rare disease, characterized by cytoplasmic inclusions of light chain immunoglobulins, in most cases in the form of crystals of kappa light chain in the endolysosomal compartment of proximal tubular cells.^[1] The most common underlying hematological disorders are low-grade multiple myeloma and a nonmalignant B cell clone.^[1,2] In the latter case, the disease is classified as monoclonal

gammopathy of renal significance.^[3,4] Proximal tubular cell function impairment may cause urinary wasting of phosphate, bicarbonate, glucose, urate, or amino acids. The presence of all of these features defines the Fanconi syndrome. Tubular secretion of creatinine occurs in the proximal tubular cells, but impairment of this secretion has never been described as a feature of the Fanconi syndrome. We report a case of LCPT without any usual sign of tubular cell dysfunction apart from mild proteinuria, but with a complete abolishment of tubular secretion of creatinine.

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2. Case report

A 39-year-old African woman was referred for the management of chronic kidney disease. She had a medical history of silicone breast implants (cosmetic purpose). Serum creatinine was 120 μmol/L, and the glomerular filtration rate estimated by the CKD-EPI equation (eGFR) was 57 mL/min/1.73 m².^[5] She had high blood pressure with no other clinical symptom. Blood analysis revealed monoclonal Immunoglobulin G κ (14 g/L) associated with free monoclonal κ light chains. Urinalysis revealed isolated tubular proteinuria (~1 g/d). There was no urinary wasting of phosphate, bicarbonate, glucose, urate, or amino acids. Bone marrow aspiration was normal (4.5% of nondystrophic plasma cells). Kidney biopsy revealed LCPT, with an appearance of osmotic nephrosis on light microscopy. These atypical histological findings have been previously reported^[6] (Fig. 1). The patient refused any chemotherapy.

Three years later, the monoclonal immunoglobulin was stable at 1.5 g/L, whereas serum creatinine was increased at 157 μmol/L.

Her treatment (nicardipine 50 mg q.d., and levothyroxine 87.5 µg q.d.) was unchanged. She was referred in our renal physiology unit for a glomerular filtration rate measurement and an assessment of tubular functions.

Measured GFR (mGFR), determined with urinary clearance of $^{51}\text{CrEDTA}$ during 6 consecutive 30-min periods, was 55 mL/min/1.73 m². This value was much higher than eGFR derived from creatinemia (40 mL/min/1.73 m²).

She had proteinuria (84 mg/mmol), composed of low-molecular-weight proteins and of light κ chains in equal proportions, but presented no other proximal tubular dysfunction: no uric acid leak (uricemia 236 µmol/L and fractional excretion 11%), phosphate wasting (phosphatemia was 1.3 mmol/L and TmPi/GFR 1.1 mmol/L), aminoaciduria, acidosis, or glycosuria.

Tubular secretion of creatinine was evaluated by the part of creatinine clearance attributable to secretion (CCr-S, calculated as creatinine clearance [CCr] – mGFR in 6 consecutive periods). We compared these data to those of 25 subjects matched for mGFR, age, sex, and ethnicity (Table 1). CCr-S was 0.5 mL/min/1.73 m², which was almost negligible and significantly lower than the mean CCr-S measured in the control population (15.3 ± 4.9 mL/min/1.73 m², $P < 0.01$).

The patient has given an informed consent for the publication of this case report. In addition, publication of anonymous data obtained in the context of clinical care regarding the topic of glomerular filtration rate has been approved by our institutional review board (IRB -00006477- of HUPNVS, Paris 7 University, AP-HP).

3. Discussion

Creatinine is freely filtered at the glomerulus, but is also actively secreted in the proximal tubule via a transcellular pathway. Creatinine crosses the basolateral membrane through the human organic cation transporter 2 (OCT2) and the apical membrane through the multidrug and toxin extrusion (MATE) transporters 1 and 2-K.^[7,8] Several drugs, such as cimetidine, trimethoprim, or some antiretroviral treatments, have been shown to inhibit its tubular secretion.^[9] These drugs cause an increase in serum creatinine of ~20% to 30%.

We describe the lack of tubular secretion of creatinine a previously unreported feature of proximal tubular dysfunction in a patient with LCPT. Importantly, the control group was matched for all factors known or suspected to influence tubular handling of creatinine, and in particular included only patients of African origin. Another unusual finding in our patient was that apart from a minor leak of low-weight proteins, and despite significant histological damage, this feature was the only sign of proximal tubular dysfunction. Such a subtle phenotype is highly atypical in LCPT-related tubulopathy, as only exceptional cases of LCPT with no feature of proximal tubular dysfunction have been reported.^[10,11] Whether creatinine tubular secretion was intact in these patients with LCPT and no obvious tubular dysfunction was not investigated.

Even though the term Fanconi syndrome is usually restricted to cases with complete dysfunction of proximal tubular transports (amino acids, glucose, phosphate, uric acid, low-weight proteins), partial or incomplete tubular dysfunction also appears to be a common finding in LCPT.^[12]

The selective impairment of a single proximal tubule transport in LCPT may actually not be unusual but largely underdiagnosed because all proximal transports are not always carefully phenotyped in clinical practice. This is even more the case for

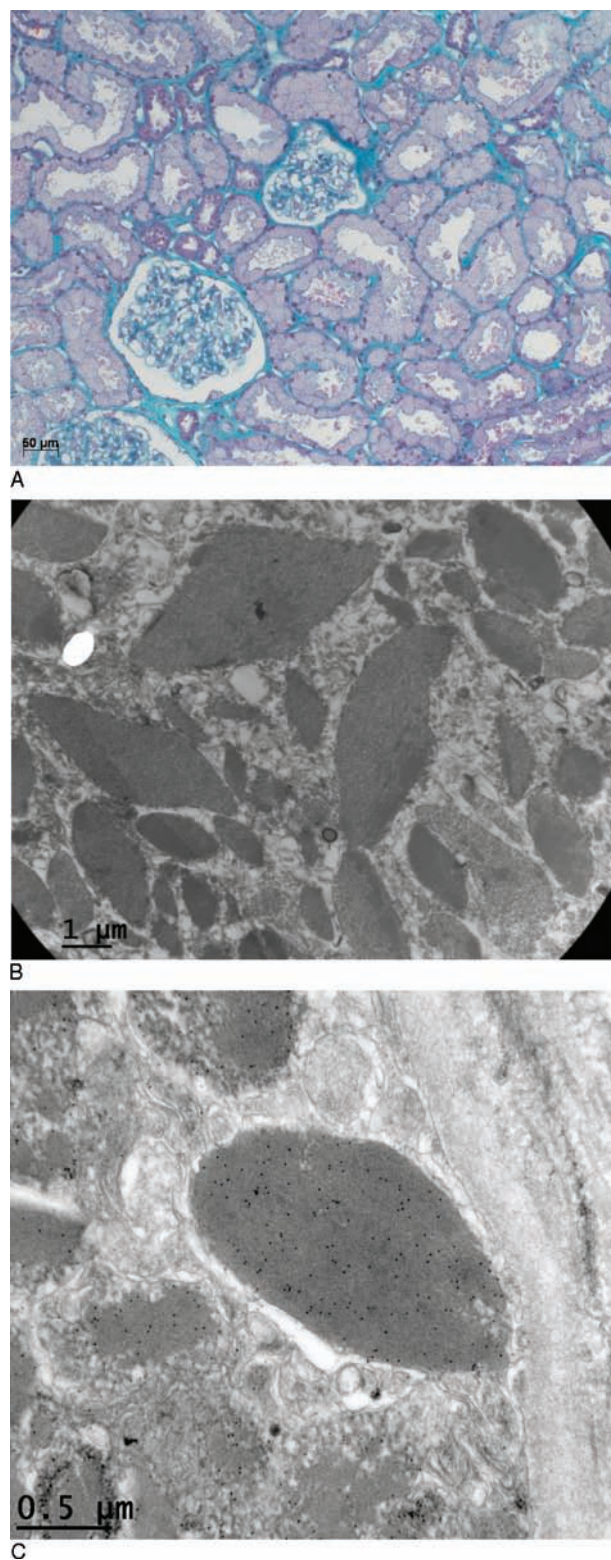


Figure 1. Kidney biopsy. (A) Light microscopy revealed a diffuse swelling of proximal epithelial cells containing clear vacuolizations suggestive of osmotic syndrome (Masson's trichrome, magnification $\times 100$). (B) Electron microscopy at a magnification of $\times 15,000$ showed numerous crystalline inclusions in the cytoplasm of proximal tubular cells. (C) Immunoelectron study of the vacuoles at a magnification of $\times 50,000$ showing positive staining with an anti- κ antibody.

Table 1
Renal handling of creatinine.

| | Patient | Controls |
|-------------------------------------|---------|--------------|
| Age | 42 | 40.6 ± 4.6 |
| SCr (μmol/L) | 157 | 105.7 ± 15.8 |
| mGFR (mL/min/1.73 m ²) | 55 | 55.2 ± 5.4 |
| CCr (mL/min/1.73 m ²) | 55.5 | 70.4 ± 8.2 |
| CCr-S (mL/min/1.73 m ²) | 0.5 | 15.3 ± 4.9 |

Data are expressed in mean ± standard deviation for the matched control populations (n=25). In the patient, the part of creatinine clearance due to tubular secretion is negligible and significantly lower than that measured in the corresponding control population, matched for mGFR, sex, age, and ethnicity. CCr = clearance of creatinine, CCr-S = part of creatinine clearance attributable to secretion, mGFR = measured glomerular filtration rate, SCr = plasma creatinine concentration.

the specific dysfunction of creatinine transport, because of the technical difficulty to measure tubular secretion of creatinine, namely the requirement of the simultaneous measurement of GFR from the urinary clearance of a tracer with an ideal renal handling (freely filtered at the glomerulus, and neither metabolized, nor secreted nor reabsorbed by the tubule) and of urinary clearance of creatinine.

Our study did not explore the underlying pathophysiological mechanisms explaining the absence of tubular creatinine secretion. One could hypothesize that the light chains endolysosomal crystals interfere with membrane trafficking of the creatinine transporters and/or with degradation of these proteins. Thus, Luciani et al have evidenced a decreased membrane expression of megalin, cubulin, and NaPi-IIa in a mouse model of LCPT.^[12] A dedicated study exploring the expression of creatinine transporters in biopsies of patients with LCPT, with various degrees of tubular dysfunction to search for a correlation with creatinine tubular secretion would be of great interest.

Our study has important clinical implications, as patients displaying this feature will have a non-GFR-related increase in plasma creatinine concentration and therefore an underestimation of eGFR from creatinine-derived formulas such as the MDRD or CKD-EPI equations. The occurrence of this proximal tubule dysfunction could lead to misjudge the severity of LCPT and could be a source of errors in drug-dose adaptation. In the present case, the expected creatinine value, had the patient displayed a tubular secretion in the mean range of the control population, was 125 μmol/L, corresponding to an eGFR-CKD-EPI value of 53 mL/min/1.73 m², much closer to mGFR than her actual eGFR value.

Moreover, interpreting the evolution of creatinine during treatment, in patients with LCPT, could be misleading, as the serum creatinine assay does not allow assessing whether changes

in serum creatinine are due to a variations in creatinine tubular transport or to a variation in GFR.

In conclusion, we report a so far undescribed feature of proximal tubule dysfunction in the setting of LCPT, namely a complete inhibition of tubular secretion of creatinine. In our patient, except for mild proteinuria this inhibition was the sole feature of a proximal tubular dysfunction. Further studies are needed to determine the prevalence of this finding in LCPT, both in forms without proximal tubular cell impairment, and in classical forms of the disease with the Fanconi syndrome, as a high prevalence of the disorder will greatly impact assessment of GFR in these patients.

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